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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,931	11/16/2005	Jose Manuel Bartolome-Nebreda	PRD2059USPCT	5571
45511 7590 12/04/2007 WOODCOCK WASHBURN LLP CIRA CENTRE, 12TH FLOOR 2929 ARCH STREET PHILADELPHIA, PA 19104-2891			EXAMINER MABRY, JOHN	
			ART UNIT 1625	PAPER NUMBER
			NOTIFICATION DATE 12/04/2007	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/556,931	<b>Applicant(s)</b> BARTOLOME-NEBRED A ET AL.	
	<b>Examiner</b> John Mabry, PhD	<b>Art Unit</b> 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 16 November 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-6 and 8-19 is/are pending in the application.
- 4a) Of the above claim(s) 9-19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |                                                                                                                                |                                                                                         |
|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                           | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>4/18/06</u> | 6) <input type="checkbox"/> Other: _____                                                |

## **DETAILED ACTION**

### ***Response to Election/Restrictions***

Applicant's response to Restriction/Elected filed November 15, 2007 is duly noted and has been fully considered. The Examiner is persuaded with Applicant's proposed alternative Restriction/Election requirement as set for in response. Examiner has rejoined all claimed alternative forms of  $-a^1=a^2-a^3=a^4$ - which consists of (a-1), (a-2), (a-3) and (a-4). It is noted that Applicant's proposed alternative Restriction/Election requirement consists of Groups I-VIII and that Applicants has elected Group II. However, the Examiner still reserves the right as set forth Restriction/Election requirement dated October 22, 2007. These rights are as follows: a) methods of treatment/prevent will be limited to the scope of one of Applicant's proposed compound/composition groups, b) an election of single disclosed species is required, and c) the method of treatment/prevention is may be subject to further restriction. These rights also apply to process of preparation group as well.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "radical" in respective claims is a relative term which renders the claim indefinite. The term "radical" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Oxford Dictionary of Chemistry defines the term "radical" as an atom or group of atoms with an unpaired valence electron. Examiner respectfully suggests the use of an appropriate and accurate term.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of Formula I, wherein  $X=CR^6$ ;  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6=H$ , halogen,  $NO_2$ , hydroxyl, cyano;  $Y=(c-1)$  and  $(c-2)$  wherein  $R^8=H$  **does not** reasonably provide enablement for compounds of Formula I, wherein  $X=N$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6$  equals to all substituents listed in claim 1;  $Y=(c-3)$ ,  $(c-4)$ ,  $(c-5)$ ,  $(c-6)$  or  $(c-7)$  and  $R^8$  equals to all substituents listed in claim 1. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims: Scope of the compounds. Owing to the range of many variables, millions of substituted indole compounds are embraced.

(2) The nature of the invention: The invention is a highly substituted substituted indole compounds.

((3) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and chemical reactivity (which is affected by determinants such as substituent effects, bonding,

molecular geometry, etc) is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(4) Direction or Guidance: That provided is very limited. Applicant shows a general synthesis of compounds of Formula I, under Preparation on page 20-25 of the Specification, but does not show the starting material used to make the variety of compounds claimed. There is limited evidence in the Specification of the example compounds that only cover a small portion of the substituents claimed of Formula I. Thus, there is no specific direction or guidance regarding said compounds of Formula I specifically mentioned in Scope.

The specification does not provide any support for the synthesis of compounds of Formula I, wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6$ =

alkyl, alkenyl, mono- or dialkylaminoalkyl, hydroxy, alkyloxy, alkylcarbonyloxy, amino, mono- or dialkylamino, formylamino, alkylcarbonylamino, alkylsulfonylamino, hydroxycarbonyl, alkyloxycarbonyl, aminocarbonyl, mono- or dialkylaminocarbonyl, alkylcarbonyloxy alkyloxycarbonyloxy, alkylthio, aryl or [[and]] heteroaryl;

where  $X=N$ ;  $Y=(c-3)$ ,  $(c-4)$ ,  $(c-5)$ ,  $(c-6)$  or  $(c-7)$  and where  $R^8$ =

- $R^8$  is ~~selected from the group consisting of~~ hydrogen, halo, alkyl, hydroxy, alkyloxy, alkylcarbonyloxy, alkyloxycarbonyloxy, hydroxycarbonyl, aminocarbonyl, mono- or dialkylaminocarbonyl, alkyloxycarbonyl or ~~[[and]]~~ amino;
- alkyl represents a straight or branched saturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic saturated hydrocarbon radical having from 3 to 6 carbon atoms; said radical being optionally substituted with at least one ~~or more~~ phenyl, halo, cyano, oxo, hydroxy, formyl or amino radical[[s]];
- alkenyl represents a straight or branched unsaturated hydrocarbon radical having from 1 to 6 carbon atoms or a cyclic unsaturated hydrocarbon radical having from 3 to 6 carbon atoms ; said radical having at least one ~~or more~~ double bond[[s]] and said radical being optionally substituted with at least one ~~or more~~ phenyl, halo, cyano, oxo, hydroxy, formyl or amino radical[[s]];
- aryl represents phenyl or naphthyl, optionally substituted with at least one ~~or more~~ radical[[s]] that is selected from the group consisting of alkyl, halo, cyano, oxo, hydroxy, alkyloxy or ~~[[and]]~~ amino ; and
- heteroaryl ~~is represents a monocyclic heterocyclic radical that is selected from the group consisting of~~ azetidiny, pyrrolidiny, dioxoly, imidazolidiny, pyrrazolidiny, piperidiny, homopiperidiny, dioxyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, imidazolidiny, tetrahydrofuranyl, 2H-pyrrolyl, pyrroliny, imidazoliny, pyrrazolinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, pyridiny, pyrimidiny, pyraziny, pyridaziny or ~~[[and]]~~ triaziny ; each radical optionally substituted with at least one ~~or more~~ radical[[s]] that is selected from the group of alkyl, aryl, arylalkyl, halo, cyano, oxo, hydroxy, alkyloxy or ~~[[and]]~~ amino;

The Specification shows very limited evidence in reference to encompassing the entire scope of the claims. Applicant shows a general synthesis of compounds of Formula I, under Preparation on page 20-25 of the Specification, but does not show the

starting material used to make the variety of compounds claimed. There is limited evidence in the Specification of the example compounds that only cover a small portion of the substituents claimed of Formula I.

The availability of the starting material that is needed to prepare the invention as claimed is at issue here...As per MPEP 2164.01 (b). A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court *in re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made it clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

(5) State of the Prior Art: These compounds are substituted indole compounds of Formula I, wherein  $X=CR^6$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6=H$ , halogen,  $NO_2$ , hydroxyl, cyano;  $Y=(c-1)$  and  $(c-2)$  wherein  $R^8=H$  which are well documented in the art. So far as the examiner is aware, no substituted indole compounds of Formula I wherein  $X=N$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6$  equals to all substituents as described above;  $Y=(c-3)$ ,  $(c-4)$ ,  $(c-5)$ ,  $(c-6)$  or  $(c-7)$  and  $R^8$  equals to all substituents as described above of any kind have been made or



used.

(6) Working Examples: Applicant shows examples Table 1, pages 26-30 but no working examples were shown wherein  $X=N$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^6$  equals to all substituents as described above;  $Y=(c-3)$ ,  $(c-4)$ ,  $(c-5)$ ,  $(c-6)$  or  $(c-7)$  and  $R^8$  equals to all substituents as described above of any kind have been made or used.

(7) Skill of those in the art: The ordinary artisan is highly skilled, e.g. a masters or PhD level chemist.

(8) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome.

Due to the level of unpredictability in the art, the very limited guidance provide, and the lack of working examples, the Applicant has shown lack of enablement for the groups noted groups on Formula I.

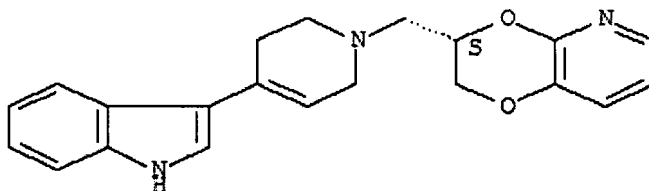
MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

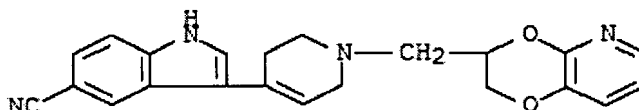
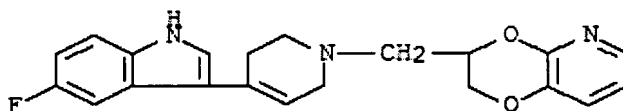
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The instant application claims compounds and pharmaceutical compositions of Formula I, wherein  $-Z^1-Z^2-$  =  $-O-CH_2-CH_2-$ ,  $(R^1)=H$ ,  $p=0$ ,  $Y=(c-2)$  wherein  $m=0$ ,  $R^5=H$ ,  $X=C$  and  $R^2, R^3, R^4=H$ .

Tran discloses compounds and pharmaceutical compositions of Formula I, wherein  $-Z^1-Z^2-$  =  $-O-CH_2-CH_2-$ ,  $(R^1)=H$ ,  $p=0$ ,  $Y=(c-2)$  wherein  $m=0$ ,  $R^5=H$ ,  $X=C$  and  $R^2$ ,  $R^3$ ,  $R^4=H$  (see Example 1, page 15).



Tran also discloses compounds and pharmaceutical compositions of Formula I, wherein  $-Z^1-Z^2-$  =  $-O-CH_2-CH_2-$ ,  $(R^1)=-F$ ,  $-CN$ ,  $p=0$ ,  $Y=(c-2)$  wherein  $m=0$ ,  $R^5=H$ ,  $X=C$  and  $R^2, R^3, R^4=H$  (see Example 2, page 16 and Example 3, page 17).



Note: Examiner acknowledges Applicants' proviso "...that compounds wherein simultaneously  $-a^1=a^2-a^3=a^4-$  is (a-4),  $-Z^1-Z^2-$  is (b-2) and Y is (c-2)..." However, said proviso encompasses a major portion of compounds in which Applicant is enabled.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

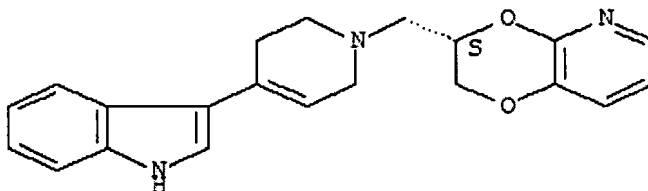
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5 and 8 are rejected under 35 U.S.C. 103(a) unpatentable over Tran et al (WO 02/085911 A1 – US Patent equivalents 6,656,950 B2 and 6,987,117 B2).

The instant application claims compounds and pharmaceutical compositions of Formula I, wherein  $-Z^1-Z^2-$  =  $-O-CH_2-CH_2-$ ,  $(R^1)=H$ ,  $p=0$ ,  $Y=(c-2)$  wherein  $m=0$ ,  $R^5=H$ ,  $X=C$ ;  $R^2$ ,  $R^3$ ,  $R^4=H$  and  $-a^1=a^2-a^3=a^4-$  =  $-CH=CH-N=CH-$  (a-3).

#### ***Scope & Content of Prior Art MPEP 2141.01***

Tran discloses compounds and pharmaceutical compositions of Formula I, wherein  $-Z^1-Z^2-$  =  $-O-CH_2-CH_2-$ ,  $(R^1)=H$ ,  $p=0$ ,  $Y=(c-2)$  wherein  $m=0$ ,  $R^5=H$ ,  $X=C$ ;  $R^2$ ,  $R^3$ ,  $R^4=H$  and  $-a^1=a^2-a^3=a^4-$  =  $-CH=CH-CH=N-$  (a-4) (see Example 1, page 15).



***Differences between Prior Art & the Claims MPEP 2141.02***

Tran differs from instant claims at the positional location of the nitrogen atom in sub-formula  $-a^1=a^2-a^3=a^4-$  of the general Formula I. Tran discloses compound wherein  $-a^1=a^2-a^3=a^4- = -CH=CH-CH=N-$  (a-4) and instant application claims compound wherein  $-a^1=a^2-a^3=a^4- = -CH=CH-N=CH-$  (a-3). These are positional isomers.

***Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413***

There is little difference between the nitrogen atom being at the position  $a^4$  as compared at the  $a^3$  position on the claimed structure of formula I. It is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be prepared by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: *Ex parte Englehardt*, 208 USPQ 343, 349; *In re Mehta*, 146 USPQ 284, 287; *In re Surrey*, 138 USPQ 67; *Ex Parte Ullyot*, 103 USPQ 185; *In re Norris*, 84 USPQ 459; *Ex. Parte Naito*, 168 USPQ 437, 439; *Ex parte Allais*, 152 USPQ 66; *In re Wilder*, 166 USPQ 545, 548; *Ex parte Henkel*, 130 USPQ 474; *Ex parte Biel*, 124 USPQ 109; *In re Petrzilka*, 165 USPQ 327; *In re Crownse*, 150 USPQ 554; *In re Fouche*, 169 USPQ 431; *Ex parte Ruddy*, 121 USPQ 427; *In re Wiechert*, 152 USPQ 249, *In re Shetty*, 195 USPQ 753; *In re Jones*, 74 USPQ 152, 154. There may be others as well. Thus, said claims are rendered obvious by Tran et al.

For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (*Englehardt*) and "Position isomerism is fact of close structural similarity" (*Mehta*, emphasis in the original). Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to prima facie obviousness"; one of those listed is "adjacent homologues and structural isomers". Position isomers are the basic form of close "structural isomers." Similar is *In re Schechter and LaForge*, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds...a known compound may suggest its analog or isomers, either geometric (cis v. trans) or position isomers (e.g. ortho v. para)." See also MPEP 2144.09, second paragraph. Further, the reference provides for the ring being substituted in any position.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

### ***Conclusion***

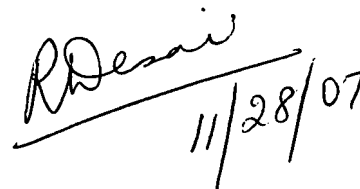
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



JM



**RITA DESAI  
PRIMARY EXAMINER**